On page 1, line 6, after "No." please insert --415,081--.

On page 1, line 7, please delete "which is" and insert therefor -all of which are-.

REMARKS

Claims 21 to 23 and 25 are currently under examination.

The title of the invention has been amended to describe Applicants' invention with greater particularity as suggested by the Examiner. In addition, the specification has also been amended to update the status of the priority documents as suggested by the Examiner.

The Examiner notes that the drawings are informal and fail to comply with 37 C.F.R. § 1.84, which indicates that a petition must be filed for photographs and color drawings to be used as formal drawings. Applicants respectfully defer responding to this objection until allowable subject matter is indicated.

Rejection under 35 U.S.C. §112, first paragraph

The rejection of claim 21 under 35 U.S.C. §112, first paragraph, is respectfully traversed.

Claim 21 is directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue comprising contacting the tissue with an anti-TGF-β antibody that binds to TGF-β; whereby the binding of the anti-TGF-β antibody to the TGF-β suppresses the deleterious accumulation of the TGF-β-induced extracellular matrix in the tissue.

Applicants respectfully submit that based on the teachings provided by the specification and that which was known in the art, the skilled artisan would have been able to practice the claimed methods without undue experimentation. Applicants agree with the Examiner that the specification provides guidance and direction regarding glomerulonephritis, ARDS, scarring and liver cirrhosis (current Office Action, page 3, first full paragraph). Applicants respectfully submit that in addition to the guidance regarding specific diseases, the specification provides guidance regarding how the skilled artisan would determine other pathologies and conditions that result from TGF-β production and extracellular matrix accumulation. In this regard, the specification teaches that the presence of elevated levels of TGF-β can be used diagnostically to determine the presence or incipient presence of pathologies deriving from extracellular matrix accumulation (page 9, lines 15-18). Moreover, the specification teaches a variety of methods for detecting the presence of elevated TGF-β levels (page 15, lines 18-26). Thus, in view of the guidance provided regarding

how to determine other pathologies and conditions that result from TGF-β production and extracellular matrix accumulation, Applicants submit that one skilled in the art would have been able to practice the invention as claimed without undue experimentation.

Applicants respectfully disagree with the assertion that there exists insufficient evidence that TGF-β plays a critical role in the deleterious accumulation of extracellular matrix in tissues in a broad range of pathogies and conditions (current Office Action, page 3, first full paragraph). In this regard, Applicants respectfully submit that glomerulonephritis is representative of a large group of diseases known as fibroproliferative diseases (reviewed in Border and Ruoslahti, J. Clin. Invest., 90:1 (1992) and Border and Noble, NEJM, 331:1286 (1994), submitted herewith as Exhibits 1 and 2, respectively). In these diseases, which include liver cirrhosis, lung fibrosis, rheumatoid arthritis and others, the mesenchymal component of the tissue expands and makes excessive extracellular matrix, obliterating the parenchymal tissue and thereby destroying organ function. There is overwhelming evidence that TGF-β is an important causative factor in these conditions, both from animal models of human disease and from humans with disease (reviewed in Border and Noble, supra(1994)).

Additional *in vivo* results have been obtained which show that inhibiting TGF-β activity suppresses cell proliferation and excessive extracellular matrix production and leads to normal tissue repair. These further *in vivo* results include, for

example, reduced pulmonary fibrosis (Giri et al., Thorax, 48:959-966 (1993); submitted herewith as Exhibit 3), reduced fibrous scar tissue and inflammation at the site of brain injury (Wahl et al., J. Exp. Med., 177:225-230 (1993); submitted herewith as Exhibit 4). Thus, it is respectfully submitted that those skilled in the art would have reasonably expected that the claimed methods employing an anti-TGF-β antibody that binds to TGF-β would be useful to decrease the deleterious accumulation of extracellular matrix associated with a pathology or a condition as set forth in claim 21. Therefore, based on the guidance provided in the specification regarding the identification of pathologies deriving from extracellular matrix accumulation and that which was known in the art, the skilled artisan would have been able to practice the claimed invention without undue experimentation. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102(e)

The rejection of claims 21, 23 and 25 under 35 U.S.C. § 102(e) as allegedly anticipated by Dasch et al., United States Patent No. 5,772,998, is respectfully traversed.

Applicants thank the Examiner for the opportunity to discuss the remaining rejections on April 19, 2000. During this telephonic interview the Examiner asserted that Applicants are required to provide additional exhibits in order to antedate the Dasch et al. patent. Particularly, the Examiner indicated that Applicants' exhibits do not establish a link between the

experiments aimed at inhibiting deleterious extracellular matrix accumulation and Applicants' claimed therapeutic methods sufficient to establish conception of the full breadth of the claimed methods.

Applicants respectfully maintain that the Rule 131 Declaration, previously submitted with the Response to Paper No. 61, provides sufficient evidence to antedate the Dasch et al. reference. Applicants respectfully submit that the law does not require Applicants to provide exhibits supporting every limitation of the claims. In this regard, the MPEP states that evidence in the form of exhibits may accompany the declaration (see MPEP §715.07). Moreover, in Ex Parte Ovshinsky, 10 USPQ 2d 1075 (Bd. Pat. App. & Inter. 1989) court states that "[a]n accompanying exhibit need not support all claimed limitations, provided that any missing limitation is supported by the declaration itself" (see also, MPEP § 715.07). In this regard, the Rule 131 Declaration by Drs. Rouslahti and Border explicitly states in paragraph 9, that the inventors contemplated, prior to December 22, 1988, anti-TGFβ antibody as an agent that could bind to and inhibit TGFβ to treat pathologies. Applicants' respectfully submit that there is no requirement to produce additional exhibits that establish Applicants' conception of therapeutic methods. Thus, Applicants Rule 131 Declaration is proper and adequate to establish the conception of therapeutic methods.

Applicants have provided five exhibits with the Rule 131 Declaration that are consistent with Applicants sworn

averments of conception of the claimed therapy methods prior to December 22, 1988. Described in detail below, each of the exhibits is directly relevant to either conception or due diligence in reduction to practice of the claimed therapy methods. Therefore, Applicants' Rule 131 Declaration previously submitted with the Response to Paper No. 61, provides sufficient evidence to antedate the Dasch et al. reference.

Nevertheless, in order to further prosecution of the claims Applicants submit as Exhibit 5, a conference abstract published for the Meeting of the American Society of Nephrology in San Antonio, Texas, which took place from December 11 to 14, 1988. This conference abstract on which Drs. Border and Rouslahti are listed as first and senior authors, respectively, is entitled "Transforming Growth Factor β (TGFβ) Uniquely Regulates Production of Glomerular Extracellular Matrix" and clearly articulates Applicants' conception of treating pathologies related to TGFβ-mediated accumulation of extracellular matrix prior to December 22, 1988.

Overall, Applicants respectfully submit that Applicants' averments in the Rule 131 Declaration and corresponding exhibits submitted previously clearly fulfill the mandate of 37 C.F.R. § 1.131(b) by showing conception of the invention prior to the effective date of Dasch et al. (December 22, 1988) coupled with Applicants' due diligence from prior to December 22, 1988 until the filing date of the above-identified application (see MPEP § 717.07). As set forth above, there is no requirement for Applicants to establish via

extrinsic evidence a link between the experiments aimed at inhibiting deleterious extracellular matrix accumulation and Applicants' claimed therapeutic methods.

Applicants respectfully disagree with the Examiner's assertion that "applicants' evidence subsequent to the priority of prior art references is rendered moot." Applicants respectfully submit that Exhibits D and E, which are dated subsequent to December 22, 1988, are proper and relevant to establishing that Applicants were diligent in their efforts leading up to the filing of the above-identified application. Under 37 C.F.R. § 1.131, the critical period in which diligence must be shown begins just prior to the effective date of the reference and ends with the date of reduction to practice, either actual or constructive. In this regard, the filing of a United States patent application represents constructive reduction to practice. Therefore, despite their date subsequent to the December 22, 1988 priority date of Dasch et al. Exhibits D and E are proper to show diligent reduction to practice based upon 37 C.F.R. § 1.131 (see also MPEP §715.07(a)).

It is further respectfully submitted that the Rule 131 Declaration submitted with Applicants' previous Response establishes that Applicants conceived of the claimed methods prior to the effective date of the '998 Dasch et al. patent, and that Applicants were diligent in reducing the claimed invention to practice. The Examiner asserts that absent a clear explanation of exactly what facts are relied on, the laboratory notebook pages provide insufficient assistance in determining

"conception, diligence and reduction to practice before the prior art" (see current Office Action, page 5, fifth full paragraph). In this regard, Applicants respectfully submit that Exhibits A through C clearly show conception and due diligence in reducing the claimed invention to practice prior to the effective date of the '998 Dasch patent. Furthermore, Exhibits D and E show Applicants' continued due diligence in reducing the claimed invention to practice leading up to the filing of the above-identified application, which is constructive reduction to practice. Applicants are not required to show reduction to practice prior to the effective date of the prior art references.

Applicants submit that the Rule 131 Declaration by Drs. Rouslahti and Border and corresponding Exhibits submitted with Applicants' previous Response of August 25, 1999 sufficiently demonstrate Applicants' conception of the invention prior to the effective date of the Dasch et al.'998 patent(December 22, 1988). Applicants respectfully disagree with the Examiner's assertion that "it appears that this evidence is directed toward characterizing the role of TGF-β in certain aspects of glomerular disease and not on the scope of the claimed methods" (see current Office Action, page 5, fifth full paragraph). Claim 21 is directed to a method of decreasing the deleterious accumulation of extracellular matrix associated with a pathology or a condition wherein TGF-β-induced production and deleterious accumulation of an extracellular matrix component in a tissue exists by contacting the tissue with an agent that binds to TGF-β. Claim 22 is directed to the same method of decreasing the

deleterious accumulation of extracellular matrix associated with glomerulonephritis.

Applicants respectfully submit that Exhibit A to the Rule 131 Declaration contains three notebook pages that show the protocol for development of a rabbit anti-TGF-β antiserum substantially as set forth in Example III.e of Applicants' specification. Applicants respectfully submit that development of anti-TGF-β antibodies is consistent with the conception of the claimed invention.

Exhibit B to the Rule 131 Declaration provides three laboratory notebook pages demonstrating experiments designed to characterize the ability of TGF-β inhibitory agents to decrease the secretion and accumulation of extracellular matrix components, specifically, decorin and biglycan in a rat glomerular culture experimental model. Because decorin and biglycan are proteoglycans that are pathologically accumulated in the extracellular matrix in a variety of pathologies including glomerulonephritis, Applicants respectfully submit that Exhibit B provides strong corroboration that Applicants' efforts were directly aimed at the claimed method of decreasing the pathologic accumulation of extracellular matrix. In this regard, page 1 of Exhibit B demonstrates the ability of anti-TGF-β antibody to inhibit the secretion of proteoglycans in the above-described rat glomerular culture model substantially as described in Examples IV and VII of Applicants' specification. Similarly, page 2 of Exhibit B demonstrates the ability of RGD peptides to inhibit the secretion of proteoglycans in a rat glomerular cell

culture model, while page 3 demonstrates the ability of platelet derived growth factor (PDGF) to inhibit the secretion of proteoglycans in a rat glomerular cell culture model. Applicants respectfully submit that the protocols submitted as Exhibit B directly relate to testing agents that could bind to TGFβ in a tissue and inhibit TGFβ effects to treat pathologies.

Exhibit C is a letter from Dr. Ruoslahti to Dr. Border, which discusses the results relating to "the inhibition of TGFβ effects by PDGF" and "the inhibition of TGFβ effects by RGD." Thus, Exhibit C further documents Applicants' conception of the claimed methods as well as their diligence in pursuing their reduction to practice. Significantly, Exhibits A through C pre-date the December 22, 1988, the effective date of the '998 Dasch et al. patent.

The Examiner asserts that it does not appear that Applicants' evidence supports the use of anti-TGF-β antibodies to inhibit the deleterious accumulation of extracellular matrix associated with glomerulonephritis. Applicants respectfully submit that the Rule 131 Declaration represents Applicants' averments under oath that the claimed therapeutic methods were conceived prior to December 22, 1988. As set forth above, given Applicants' sworn averments in this regard, there is no additional requirement for Applicants to establish via extrinsic evidence a link between the experiments aimed at inhibiting deleterious extracellular matrix accumulation and Applicants' claimed therapeutic methods. Moreover, as stated in Applicants' previous Response, Dr. Border was an attending physician of

glomerulonephritis patients prior to his work on the instant invention, during his work on the present invention, and continues to treat such patients to date. The purpose of Dr. Border's collaboration with Dr. Ruoslahti was to identify new methods of treating patients with such pathologies. Nevertheless, as set forth above, provided as Exhibit 5 is a national conference abstract that clearly articulates Applicants' conception of treating pathologies related to TGFß-mediated accumulation of extracellular matrix prior to December 22, 1988. Therefore, Applicants respectfully submit that conception of the claimed therapeutic methods prior to December 22, 1988 has been adequately demonstrated.

Regarding the issue of due diligence in reducing the claimed invention to practice, Applicants respectfully submit that in addition to Applicants' sworn averments in this regard, Exhibits A through E to the Rule 131 Declaration chronicle Applicants' diligent efforts, which culminated in the filing of the above-identified application. Exhibits A and B to the Rule 131 Declaration, described above, provide evidence of the scientific protocols aimed at reducing the claimed invention to practice. The chronicled efforts are consistent with and support Applicants' averments regarding their diligent pursuit of the claimed methods. Furthermore, Exhibit C to the Rule 131 Declaration, a letter from Dr. Ruoslahti to Dr. Border mailed prior to December 22, 1988, shows that Applicants' were actively pursuing the experiments described in Exhibit B, which were central in reducing the claimed methods to practice.

Exhibits D and E to the Rule 131 Declaration provide further evidence that Applicants were diligently pursuing the reduction to practice of the claimed methods. As set forth in Applicants' previous Response, the excerpts of a grant application submitted as Exhibit D to the Rule 131 Declaration document Applicants' diligent pursuit of scientific studies immediately applicable to the design of a study to treat humans with glomerulonephritis. Similarly, Exhibit E to the Rule 131 Declaration documents excerpts of initial draft manuscript titled "An Antiserum Against Transforming Growth Factor β Suppresses Experimental Glomerulonephritis" and represents further evidence properly considered in determining Applicants' due diligence in reducing the claimed methods to practice. As set forth above, the critical period in which diligence must be shown begins just prior to the effective date of the reference and ends with the date of a reduction to practice, either actual or constructive. Furthermore, the filing of a United States patent application represents constructive reduction to practice.

In their Rule 131 Declaration Applicants attest under oath to the fact that they conceived the claimed methods prior to December 22, 1988, and pursued the claimed methods with due diligence from prior to December 22, 1988 until the filing date of the above-identified application. Exhibits A through E to the Rule 131 Declaration corroborate Applicants' sworn averments through numerous documents, all of which are relevant to establishing conception and due diligence in the pursuit of reducing the claimed methods to practice. Applicants respectfully submit that in light of the arguments and Exhibit 5

set forth above, the Rule 131 Declaration and corresponding Exhibits A through E previously submitted, conception of the claimed methods prior to the effective date of Dasch et al. (December 22, 1988) as well as due diligence in reducing the claimed methods to practice from prior to December 22, 1988 until the filing date of the above-identified application has been adequately demonstrated. Therefore, the Dasch et al. '998 patent cannot anticipate the claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103(a)

The rejection of claims 21 and 22 under 35 U.S.C. §103(a) as allegedly unpatentable over Dasch et al., supra, in view of Ruoslahti et al. (U.S. Patent 5,583,103) and/or Bassols et al., J. Biol. Chem., 263:3039-3045 (1988) is respectfully traversed.

Applicants respectfully submit that Applicants may overcome a 35 U.S.C § 103 rejection based on a combination of references by showing completion of the invention prior to the effective date of any of the references. Furthermore, Applicants need not antedate the reference with the earliest filing date. Applicants respectfully submit that in light of the arguments and Exhibit 5 set forth above, the Rule 131 Declaration and corresponding Exhibits A through E previously submitted, conception of the claimed methods prior to the effective date of Dasch et al. (December 22, 1988) as well as due diligence in

reducing the claimed methods to practice from prior to December 22, 1988 until the filing date of the above-identified application has been adequately demonstrated. Therefore, the claimed invention is unobvious over over Dasch et al. in combination with either or both of Ruoslahti et al. and Bassols et al. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: May 5, 2000

Robert T. Ramos
Registration No. 37,915
Telephone: (619) 535-9001
Facsimile: (619) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive, Suite 700
San Diego, California 92122
USPTO Customer No. 23601